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The association between microscopic colitis and celiac disease: a systematic review and meta-analysis

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Abstract

Background Multiple studies suggested that celiac disease (CD) may be associated with microscopic colitis (MC); however, most were limited by a small sample size or the main scope of interest. We aimed to analyze previously published literature on this association to determine its extent and significance.

Methods A systematic review was conducted in PubMed, Embase, PubMed Central, Cochrane, and ScienceDirect databases from inception through January 2022. The PRISMA guideline was followed for data extraction. Effect estimates were extracted and combined using random effect, the generic inverse variance method of DerSimonian and Laird and pooled odds ratio (OR), and event rates (ER) were calculated. The Newcastle-Ottawa scale was used to evaluate the risk of bias. Forest plots were generated and publication bias assessed via conventional techniques.

Results Twenty-six studies with a total of 22,802 patients with MC were included in this analysis. CD was significantly associated with MC (odds ratio [OR] 8.276, 95% confidence interval [CI] 5.888-11.632; P<0.001). The ER for MC in CD patients was 6.2% (95%CI 4.1-9.2%; P<0.001), while the ER for CD in MC patients was 6.1% (95%CI 3.9-9.5%; P<0.001). CD was prevalent in both types of MC: 5.2% (95%CI 2.2-12.1%; P<0.001) in collagenous colitis and 6.3% (95%CI 3.4-11.5%; P<0.001) in lymphocytic colitis. We found no publication bias, according to funnel plots and Egger's regression asymmetry testing.

Conclusions Our meta-analysis confirms a statistically significant association between CD and MC, with a high prevalence of CD in both types of MC. Gastroenterologists should be wary of this association when evaluating patients with either disease, particularly patients with a suboptimal response to first-line therapy.

Keywords Microscopic colitis, celiac disease, lymphocytic colitis, collagenous colitis, autoimmune diseases

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Conflict of Interest: None

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Introduction

Microscopic colitis (MC) is an inflammatory condition in which patients suffer from chronic diarrhea with evidence of chronic inflammation under the microscope, but show normal colonic morphology macroscopically [1]. MC was first suggested as a cause of chronic diarrhea of an unknown etiology by Read *et al* in 1980 [2]. MC piqued our interest, given the normal endoscopic findings [3,4], and since then there have been many advances in characterizing and classifying MC. MC is subclassified into collagenous colitis (CC) and lymphocytic colitis (LC). LC is diagnosed with intraepithelial lymphocytes

elevated to at least >20 lymphocytes per 100 cells, without distortion of crypt architecture. CCs differ histologically, showing a more than 10-μm collagen band in the subepithelial layer, absent in LC [5,6]. Since the 2 variants overlap in clinical presentation, presumed pathophysiology and clinical course [7,8], they were eventually joined into one disease entity, MC.

MC is not an uncommon disease. A meta-analysis by Tong *et al* found pooled incidence rates of 4.14 and 4.85 per 100,000 person-years for CC and LC, respectively. The same study also showed that MC is more common in females than males, with an incidence ratio of 3.05:1 for CC and 1.92:1 for LC. The median age of onset is approximately 65 years for CC and 62 years for LC [9-11]. The exact pathogenesis and development of MC are still poorly understood, but multiple studies have suggested an association between MC and multiple different autoimmune diseases within the gastrointestinal (GI) tract, as well as in other organ systems, with the suggestion that these conditions share a similar underlying pathophysiology [12,13]. Type 1 diabetes mellitus and autoimmune thyroiditis are autoimmune diseases that are commonly concurrent with MC outside the GI tract [1,14]. Different studies have also shown some correlation between MC and multiple lymphocytic inflammatory disorders of the GI tract, including lymphocytic esophagitis, lymphocytic gastritis, duodenal intraepithelial lymphocytosis, and celiac disease (CD) [15,16]. Koskela *et al* showed that tumor necrosis factor (TNF) α and human leukocyte antigen (HLA) DR3-DQ2 haplotype have a role in the pathogenesis and development of MC, and suggested a strong association of MC with CD and other autoimmune lymphocytic disorders [1,7,14,15,17]. Other studies have shown elevated levels of interferon (IFN) γ, interleukin (IL) 15, TNF, and nitric oxide synthase levels in MC, proposing that the dysfunctional activation of the immune system and immunological pathophysiology are similar to other autoimmune diseases [18].

Furthermore, Westerlind *et al* and Stahl *et al* investigated the association between MC variants, CC and LC, and certain HLA regions in the human genome, where it was found that patients with specific HLA variants, such as HLA-B*08:01, HLA-DRB1*03:01 and HLA-DQB1*02:01, have greater risk of developing CC, while HLA-DRB1*04:01 has a protective effect against CC [19,20]. These findings helped towards a better understanding of the pathophysiology and immunogenicity of MC and suggests that MC can be related to other autoimmune diseases where specific HLA alleles are important or associated with disease development, such as CD and inflammatory bowel disease. Westerlind *et al* also studied whether there is any association between LC and specific HLA alleles, similar to those with CC, but found none; accordingly, they suggested that HLA association can differentiate between CC and LC, which may suggest differences in pathophysiological development [21].

CD is an immune-mediated disease of the small bowel attributable to gluten sensitivity in susceptible patients [12,22]. It is characterized by chronic diarrhea, malabsorption, weight loss, bloating, abdominal pain, and, as a result, failure to thrive [23,24]. CD is diagnosed by the presence of clinical symptoms, serological markers and histological examination of intestinal biopsies [25-29]. Histological evaluation typically shows a spectrum of disease, ranging from intraepithelial lymphocytosis to total mucosal damage characterized by atrophy and loss of villi, hyperplasia of the crypts and increased apoptosis of the epithelium [30-32]. The pathogenesis of CD includes gluten antigen presented on the surface of HLA complexes, mainly of haplotypes DQ2 or DQ8 [17,33,34].

Although multiple studies have proposed that MC and CD show significant correlation and have similar pathophysiological development, these studies were limited by their small sample sizes or scope of interest [35,36]. Establishing an association between such immune-mediated diseases would suggest a need for screening of concomitant pathologies, or altering the management of these patients, especially if they fail to respond to first-line therapy. Therefore, we conducted a broad-based systematic review and meta-analysis to study the association between MC and CD.

Materials and methods

Literature search and study selection

A comprehensive broad-based literature search in PubMed Central, PubMed, Embase, Cochrane, and ScienceDirect databases, from inception through January 2022, was conducted to identify all observational studies examining the association between MC and CD. The following keywords were used in different combinations: microscopic colitis, collagenous colitis, lymphocytic colitis, celiac disease, celiac sprue, autoimmune, enteropathy. Our search was limited to human studies only, but was not confined to any language, or region.

Data extraction and quality assessment

We included studies that evaluated the association between MC and CD if they presented an odds ratio (OR) for our main outcome with a 95% confidence interval (CI), or an event rate for our outcomes, or presented data sufficient to calculate these variables. Studies were excluded if they were letters to editors, case reports, case series, review articles or if they provided insufficient information to calculate the event rates and/or the OR for our main outcome.

The authors (LA and FN) performed the literature review independently. The data extracted from the studies included

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first author, year of publication, country, study design, and quantitative estimates, including event rates or ORs with 95%CIs for the association of MC with CD. The risk of internal bias was assessed using the Newcastle-Ottawa scale [37].

Statistical analysis

Statistical analysis was performed using the comprehensive meta-analysis (CMA) software, version 3 (BioStat, Inc., Eaglewood, NJ, USA). Effect estimates from the individual studies were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird [38]. A random-effect model was used, as a high probability of between-study variance, due to variations in study population and methodology, was suspected. A pooled event rate or pooled OR was calculated. A Cochran's Q-test was used to evaluate heterogeneity and quantify variation across the selected studies [39]. A funnel plot was then created to evaluate for publication and other reporting biases. The plot was examined visually for asymmetry and an Egger test for asymmetry was also conducted.

Results

Search results

The PRISMA study flowchart is shown in Fig. 1. A total of 367 articles were retrieved. After review of titles and abstracts, 310 articles were excluded as they did not meet the eligibility criteria, leaving 57 articles for full-text review. A further 31 articles were excluded, because 17 did not include the necessary data, 8 were case series and 6 had no full text available for review. This left 6 cross-sectional studies, 15 cohort studies and 5 case-control studies to be included in the analysis [11,13-16,40-60].

Study characteristics

Table 1 summarizes the studies that assessed the event rates of CD in patients with MC, and Table 2 summarizes those that assessed the event rates of MC in patients with CD. A total of 26 studies were published between the years 1997 and 2021. Seven studies were conducted in the United States [14,15,47,50,55,59,60], 4 in Sweden [11,16,48,52], 3 in Canada [41,42,54], 3 in the United Kingdom [43,57,58], 3 in The Netherlands [45,53,56], 1 in Finland [46], 1 in Hungary [40], 1 in Italy [51], 1 in Ireland [49], 1 in Denmark [13], and 1 in Spain [44]. A total of 4640 study participants were included. A case-control study by Wildt *et al*, conducted in Denmark in 2021, included the largest number of cases, more than 15,500 in total [13].

Association of MC and CD

In our meta-analysis, we have found that CD is significantly associated with MC, with pooled OR 8.276 (95%CI 5.888-11.632; P<0.001) (Fig. 2). A total of 22571 MC cases were included, of which 513 patients were found to have concurrent CD with a pooled event rate for CD in patients with MC of 6.1% (95%CI 3.9-9.5%; P<0.001), Fig. 3. CD was also found to be prevalent in both subtypes of MC individually; with a pooled event rate of 5.2% (95%CI 2.2-12.1%; P<0.001) in patients with CC (Fig. 4), and 6.3% (95%CI 3.4-11.5%; P<0.001) in patients with LC (Fig. 5).

A total of 3593 CD cases were included, of which 231 patients were found to have concurrent MC, with a pooled event rate for MC in patients with CD of 6.2% (95%CI 4.1-9.2%; P<0.001) (Fig. 6). When both subtypes of MC were evaluated individually in patients with CD, it was found that CC and LC were prevalent in CD; with pooled event rate of 1.6% (95%CI 0.7-3.5%; P<0.001) in CC (Fig. 7), and 4.3% (95%CI 3.1-5.9%; P<0.001) in LC (Fig. 8).

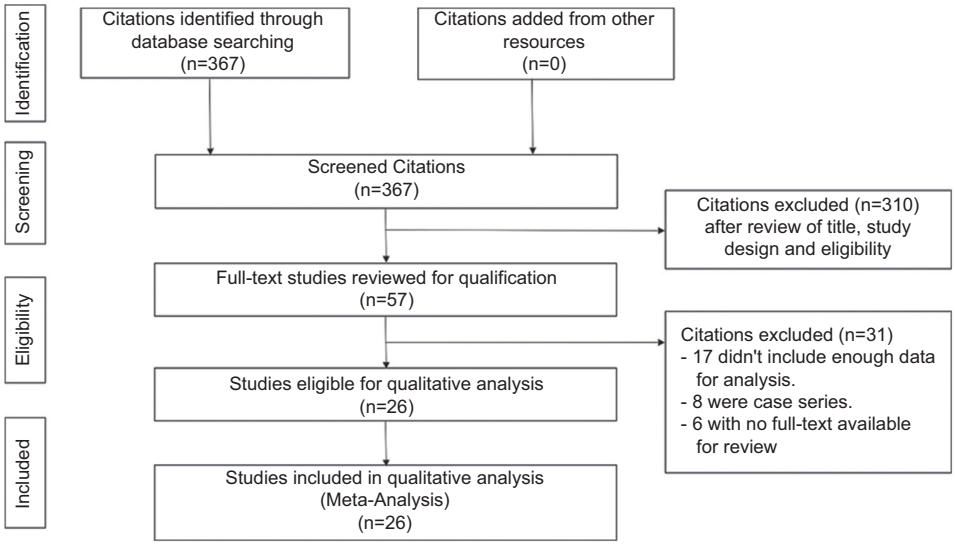

Figure 1 PRISMA study flowchart

Table 1 Summary of studies assessing celiac disease event rate in patients with microscopic colitis

Study [ref.]	Type of study	Origin, year of the study	CD cases	MC cases	OR/RR/SMR (CD in MC)	P-value for OR/RR/SMR	Event rate	P-value for event rate
Barta *et al* [40]	Retrospective cohort study	Hungary, 2005	2	53	N/A	N/A	0.038 (0.009-0.139)	0.001
Freeman *et al* [41]	Retrospective cohort study	Canada, 2004	8	36	N/A	N/A	0.222 (0.115-0.385)	0.002
Gillet *et al* [42]	Cross-sectional study	Canada, 2000	4	23	N/A	N/A	0.174 (0.067-0.382)	0.005
Green *et al* [43]	Retrospective cohort study	UK, 2019	16	483	OR 7.7 (4.7-12.6)	<0.001	0.033 (0.020-0.053)	0.001
Guagnozzi *et al* [44]	Case-control study	Spain, 2015	6	46	OR 15.3 (3.7-63.4)	<0.001	0.130 (0.060-0.261)	0.001
Jobse *et al* [45]	Retrospective cohort study	Netherlands, 2009	2	83	N/A	N/A	0.024 (0.006-0.091)	0.001
Kao *et al* [14]	Retrospective cohort study	USA, 2009	18	547	N/A	N/A	0.033 (0.021-0.052)	0.001
Koskela *et al* [46]	Case-control study	Finland, 2004	14	84	OR 16.6 (2.2-127.5)	0.007	0.167 (0.101-0.262)	0.001
Matteoni *et al* [47]	Cross-sectional study	USA, 2001	4	46	N/A	N/A	0.035 (0.013-0.091)	0.001
Mellander *et al* [11]	Retrospective cohort study	Sweden, 2016	48	795	N/A	N/A	0.060 (0.046-0.079)	0.001
Olesen *et al* [48]	Retrospective cohort study	Sweden, 2004	17	199	N/A	N/A	0.085 (0.054-0.133)	0.001
O'Toole *et al* [49]	Retrospective cohort study	Ireland, 2014	26	222	N/A	N/A	0.117 (0.081-0.166)	0.001
Pardi *et al* [50]	Retrospective cohort study	USA, 2002	10	170	N/A	N/A	0.059 (0.032-0.106)	0.001
Wildt *et al*[13]	Case-control study	Denmark, 2021	180	15597	OR 10.15 (8.20-12.6)	<0.001	0.012 (0.010-0.013)	0.001
Simondi *et al* [51]	Retrospective cohort study	Italy, 2010	4	80	N/A	N/A	0.05 (0.019-0.126)	0.001
Sonnenberg *et al* [15]	Cross-sectional study	USA, 2018	109	3456	RR 6.06 (5.06-7.25)	<0.001	0.032 (0.026-0.038)	0.001
Svensson *et al* [52]	Retrospective cohort study	Sweden, 2018	12	200	N/A	N/A	0.060 (0.034-0.103)	0.001
Verhaegh *et al* [53]	Case-control study	The Netherlands, 2017	6	171	OR 10.86 (1.3-91.4)	0.028	0.035 (0.016-0.076)	0.001
Vigren *et al* [16]	Retrospective cohort study	Sweden, 2013	15	116	N/A	N/A	0.129 (0.079-0.203)	0.001
Williams *et al* [54]	Retrospective cohort study	Canada, 2008	12	164	RR 7.9 (4.0-14.2)	<0.001	0.073 (0.042-0.124)	0.001
All CD in MC			513	22571	8.276 (5.888-11.632)	<0.001	0.061 (0.039-0.095)	0.001

CD, celiac disease; MC, microscopic colitis; OR, odds ratio; RR, relative risk; SMR, standardized mortality/morbidity risk; USA, United States of America; UK, United Kingdom; N/A, not available

Evaluation for publication bias

To evaluate for the presence of publication bias a funnel plot was generated to evaluate the association between MC and CD (Fig. 9,10). The plot for all studies is symmetric and does not suggest the presence of publication bias. Egger's regression asymmetry testing was also performed to demonstrate no evidence of publication bias (P=0.79).

Table 2 Summary of studies assessing microscopic colitis event rate in celiac disease patients

Study [ref.]	Type of study	Origin of the study	MC cases	CD cases	OR/RR/SMR (MC in CD)	P-value	Event rate	P-value
Green *et al* [55]	Cross-sectional study	USA, 2009	44	1009	SMR 45.5 (27.7-63.3)	<0.05	0.044 (0.033-0.058)	<0.001
Spijkerman *et al* [56]	Cross-sectional study	The Netherlands, 2016	20	412	N/A	N/A	0.049 (0.032-0.074)	<0.001
Dewar *et al* [57]	Prospective cohort study	UK, 2012	11	100	N/A	N/A	0.110 (0.062-0.188)	<0.001
Leeds *et al* [58]	Case-control study	UK, 2007	5	305	N/A	N/A	0.016 (0.007-0.039)	<0.001
Leffler *et al* [59]	Cross-sectional study	USA, 2007	6	113	N/A	N/A	0.053 (0.024-0.113)	<0.001
Sonnenberg *et al* [15]	Cross-sectional study	USA, 2018	134	1576	N/A	N/A	0.085 (0.072-0.100)	<0.001
Fine *et al* [60]	Prospective cohort study	USA, 1997	11	78	N/A	N/A	0.141 (0.080-0.237)	<0.001
All MC in CD			231	3593	N/A	N/A	0.062 (0.041-0.092)	<0.001

CD, celiac disease; MC, microscopic colitis; OR, odds ratio; RR, relative risk; SMR, standardized mortality/morbidity risk; USA, United States of America; UK, United Kingdom; N/A, not available

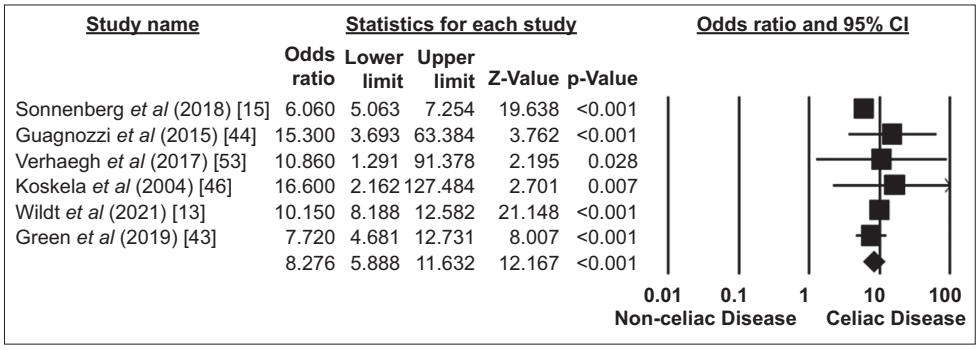

Figure 2 Forest plot of the meta-analysis of the odds ratio for celiac disease in patients with microscopic colitis

Discussion

Chronic diarrhea is defined as soft stool consistency and/or increased stool frequency with stool volume of more than 200 g/24h [61]. Chronic diarrhea is a very common complaint that patients present with to the primary care or gastroenterology clinics; it can be very unpleasant and debilitating. In many cases, patients undergo an extensive workup in order to discover the etiology, including multiple endoscopies and frequent repeat imaging [62]. The initial workup includes complete blood count, thyroid-stimulating hormone levels, basic metabolic profile, stool for occult blood, infectious workup as indicated, CD serologies, fecal calprotectin and inflammatory markers [63]. Despite an extensive workup and multiple treatments, some patients continue to suffer from chronic diarrhea without significant improvement. Many patients have also been found to have multiple concomitant pathologies, which might lead to persistence of symptoms regardless of the treatment of a single etiology. Accordingly, we studied the association between 2 common causes of chronic diarrhea, MC and CD.

The present study is the first systematic review and meta-analysis to summarize the results of all available observational studies that reported an association between MC and CD. In this meta-analysis, we found that CD was significantly associated with MC (OR 6.221, 95%CI 3.828-10.108; P<0.001). The pooled event rate for MC in patients with CD was 6.7% (95%CI 4.4-10.0%; P<0.001), while the pooled event rate for CD in patients with MC was 7.7% (95%CI 4.6-12.6%; P<0.001). CD was prevalent in both types of MC: 5.4% (95%CI 1.3-20%; P<0.001) for CC and 9.1% (95%CI 4.5-17.3%; P<0.001) for LC. The study by Sonnenberg *et al* (2018) was the largest cross-sectional study included in our analysis, involving 3456 patients with MC, 1864 with the LC subtype and 1592 with the CC subtype [15].

The underlying mechanism of the association between MC and CD is still unclarified. Some studies have suggested that the diseases have very similar immunological development, as

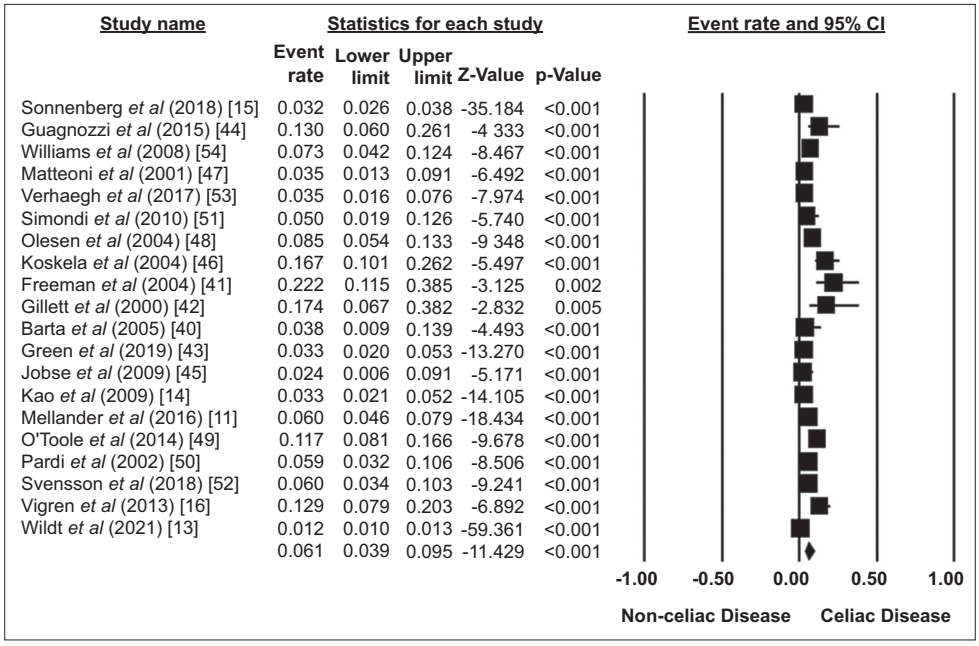

Figure 3 Forest plot of the meta-analysis of the event rates for celiac disease in patients with microscopic colitis

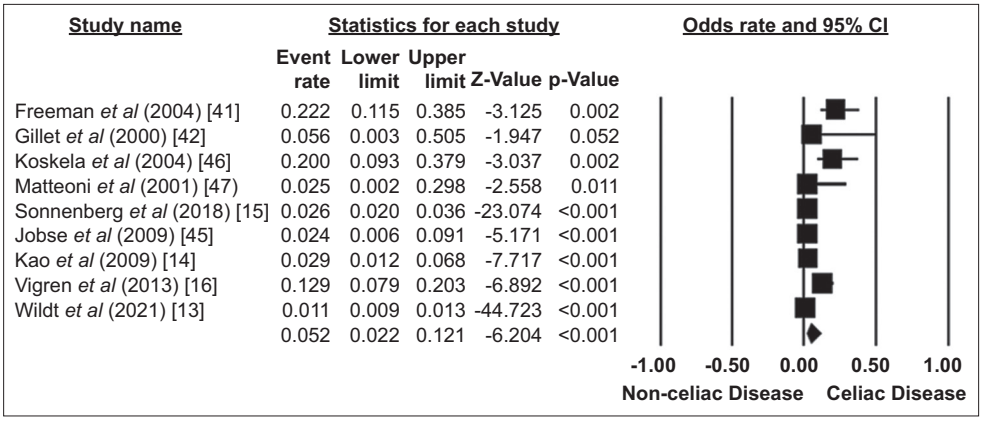

Figure 4 Forest plot of the meta-analysis of the event rates for celiac disease in patients with collagenous colitis

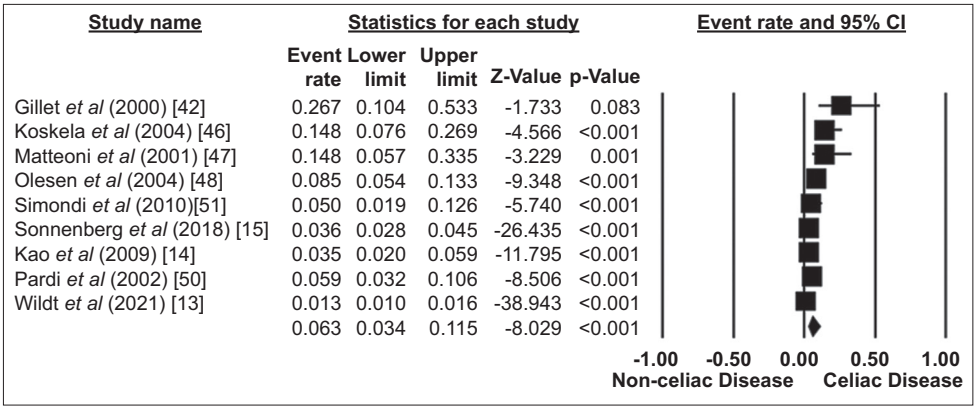

Figure 5 Forest plot of the meta-analysis of the event rates for celiac disease in patients with lymphocytic colitis

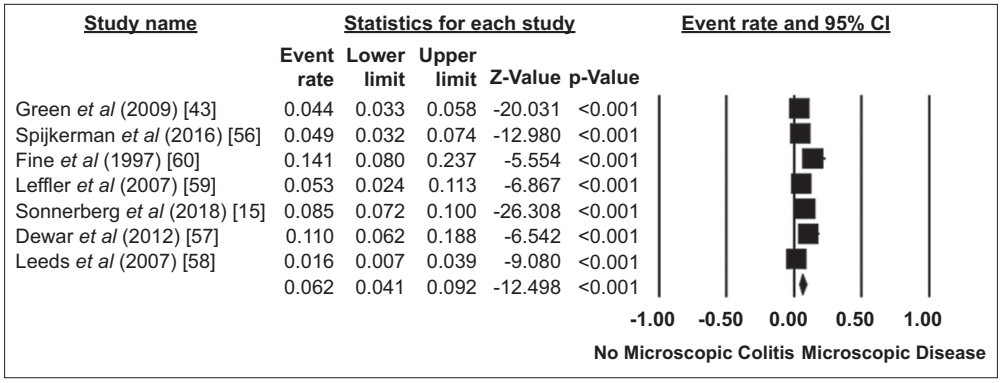

Figure 6 Forest plot of the meta-analysis of the event rates for microscopic colitis in patients with celiac disease

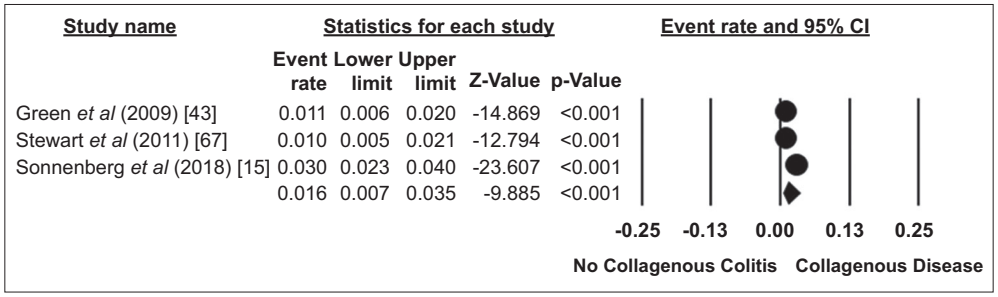

Figure 7 Forest plot of the meta-analysis of the event rates for collagenous colitis in patients with celiac disease

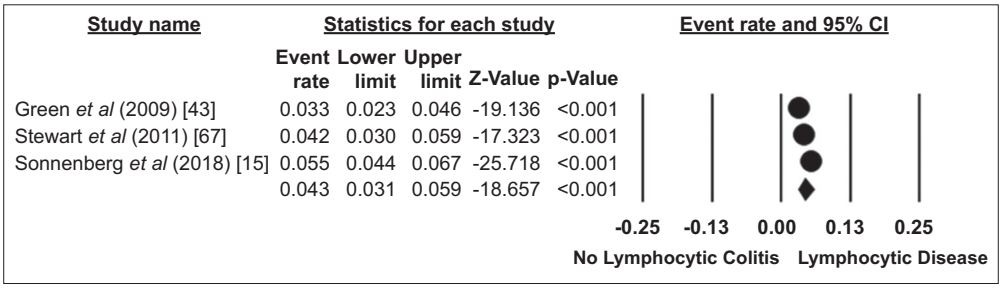

Figure 8 Forest plot of the meta-analysis of the event rates for lymphocytic colitis in patients with celiac disease

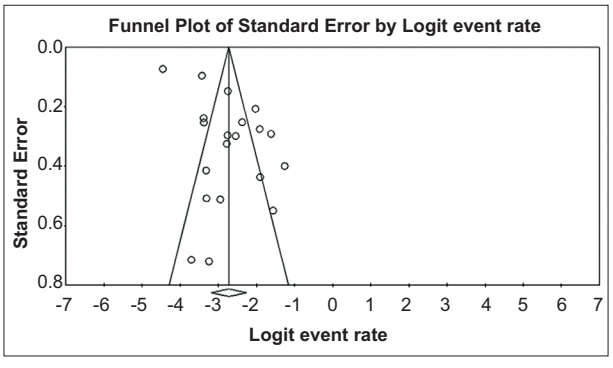

Figure 9 Funnel plot of the meta-analysis of the risk of celiac disease in patients with microscopic colitis

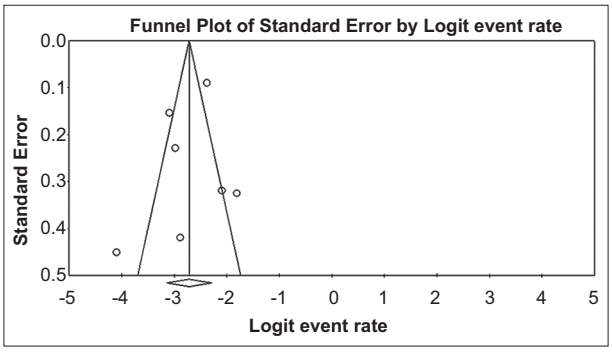

Figure 10 Funnel plot of the meta-analysis of the risk of microscopic colitis in patients with celiac disease

both are associated with elevated levels of certain inflammatory markers and specific cytokines, including IFN-γ, TNF, and IL-15. Other studies have found similar HLA complexes involved in the development of both diseases and have suggested an association between CD and MC.

As reported in the literature, immune-mediated diseases are frequently found concomitantly [64,65]. It is also well-established in the literature that most immune diseases are more common in females [66].

The 8 studies in our meta-analysis included largely diverse populations from different continents, suggesting that, even with the genetic and environmental variations among different populations, there is still a significant association between MC and CD. This also reinforces the theory that similar immunological evolution led to the emergence of both diseases. Although most patients with CD usually respond to treatment, a subset of patients partially respond or continue to have similar symptoms despite strict dietary modification. Similarly, in MC a large number may respond to first-line therapy, while others may not. In such patients with refractory disease, a second concomitant pathology should be suspected and investigated accordingly. Thus, establishing an association between MC and CD might be practice-changing and even life-changing.

In summary, our meta-analysis confirms a statistically significant association between CD and MC, with a high prevalence of CD in both subtypes of MC. Gastroenterologists should be wary of this association when evaluating patients with either disease, particularly in patients with a suboptimal response to first-line therapy.

Summary Box

What is already known:

- Microscopic colitis (MC) can cause chronic diarrhea and is diagnosed by histopathology showing large numbers of intraepithelial lymphocytes, with more than 20 lymphocytes per high power field
- MC is subdivided into collagenous and lymphocytic colitis
- MC is associated with autoimmune diseases
- Celiac disease (CD) is an autoimmune disease secondary to gluten sensitivity and can cause chronic diarrhea, malabsorption, weight loss, and bloating

What the new findings are:

- MC is significantly associated with CD
- The pathophysiology of MC can be similar to that of other autoimmune disease, such as CD, given this significant association
- Patients with chronic diarrhea who show a suboptimal response to first-line therapy should be investigated for a secondary process

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